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In Silico Identification of Potential Inhibitors from Rumex Vesicarius Against DPP4 of Diabetes Mellitus

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***Abstract*---**Given the global epidemic of type-2 diabetes mellitus (T2DM) infection and the lack of suitable therapeutic options for diabetics, only a few medications have been licensed for the treatment of infected patients. Newer anti-diabetic medications with innovative mechanisms of action, as well as ways to reduce attrition in the early stages of drug development, are urgently needed. Rumex vesicarius was tested for antibacterial and antioxidant properties. Hence far, no in silico anti-diabetic study has been published against DPP4, so the goal of this paper is to report on the in silico docking of phytochemicals found in this plant against the target DPP4. On a series of known Rumex vesicaris compounds, in silico anti-T2DM lead prioritization was done. Using Autodock 4, the docking of DPP4 with 12 phytochemical compounds was done. Twelve compounds (Apigenin, Chrysophanol, Emodin, Physcion, Catechin, Epicatechin, Luteolin, quercetin, Rhein, tetramethylene sulfone,

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alloaromadendrene, and cis-Limonene oxide) were docked into DPP4 in the present study, and one compound, Chrysophanol, showed a high binding score (-8.99 PHE:559 may have a crucial function in the binding of these compounds.

***Keywords*---**chrysophanol, diabetes mellitus, docking, DPP4, Rumex vesicarius.

Introduction

Diabetes is a rapidly spreading chronic metabolic illness that affects people all over the world. According to the International Diabetes Federation's (IDF) most recent estimates, around 425 million adults had diabetes in 2017, with the figure expected to climb to 700 million by 2045(IDF 2017). Type 2 diabetes mellitus (T2DM) increases the risk of various micro- and macro-vascular consequences, including stroke, retinopathy, neuropathy, nephropathy, coronary artery disease, hypertension, and peripheral vascular disease (Kannel et al.,1979). Insulin resistance and insulin insufficiency are the most common symptoms of T2DM. The ultimate goal of T2DM treatment is to keep glycosylated haemoglobin levels below 7% and thereby avoid the micro- and macro-vascular problems that come with the condition (Stein et al., 2013). Biguanides, insulin sensitisers (thiazolidinediones), insulin secretagogues (sulphonylureas; meglitinides), and external insulin delivery (insulin mimics) are all commonly used to lower blood glucose levels and the dangers associated with T2DM.

Currently, the Drug Administration and the European Medicines Agency have approved -glucosidase inhibitors, glucagon-like peptide-1(GLP-1) agonists, sodium-dependent glucose transporters 2 inhibitors, and the newly introduced dipeptidyl peptidase-4 (DPP-4) inhibitors (He, Z.X et al., 2015). DPP-4 (CD26, EC 3.4.14.5) is a serine peptidase that is expressed on the surface of diverse cell types as a 220 kDa homodimeric type II transmembrane glycoprotein (Rasmussen et al., 2003). Most tissues, including the kidney, gastrointestinal tract, biliary tract, and liver, as well as the placenta, uterus, prostate, skin, and lymphocytes, express it (Drucker et al., 2003). DPP-4 is implicated in rapidly inactivating both GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), resulting in GLP-1 and GIP half-lives of less than 2 minutes and 2–3 minutes, respectively (Wu, T.Z et al., 2016). GLP-1 is a 30-amino-acid peptide hormone produced by intestinal epithelial endocrine cells (Holst et al., 2007), whereas GIP is a 42-amino-acid peptide hormone produced mostly by duodenal K cells in the proximal small intestine (Ebert et al., 1987). GLP-1 and GIP work together to boost insulin production, stimulate beta cell proliferation, and minimize beta cell apoptosis, all of which help to keep postprandial glucose excursions to a minimum. As a result, GLP and GIP are involved in the anti-hyperglycemic impact of DPP-4 inhibitors. DPP-4 inhibitors have been shown to prevent the inactivation of the incretin hormone GLP-1, resulting in insulin secretion stimulation, glucagon secretion inhibition, and improved glucose management. This is a glucose-dependent mechanism that explains why DPP-4 inhibitors have a minimal risk of hypoglycemia (Farngren et al., 2014).

Rumex vesicarius L. is a member of the Polygonaceae family, which is also known as the smartweed, buckwheat, or knotweed family. There are 1120 species in 50 genera that are found all over the world, mostly in temperate and tropical climates. In India, there are around 121 species and 29 variants (including exotics) divided into 12 genera. Rumex L. contains approximately 200 species that are found in temperate climates, European countries, America, Asia, and Australia continents (Heywood et al.1978, Qaiser, M. 2001, Sanchez, I et al. 2008, Chase, M et al. 2009), with 22 species found in India. R. vesicarius L. is an annual semi-succulent plant with a pale green color and a height of 15-30 cm. It is monoecious, branching from the base, glabrous, and dichotomously branched. The plant has been shown to help with biliary diseases and cholesterol management (Davella, R et al. 2021, Al- Quran S 2009, Elegami AA et al. 2001, Rahman MA et al. 2004, Abutbul et al. 2005, Prasuna CP et al. 2009). Rumex vesicarius was tested for antibacterial and antioxidant properties. Hence far, no in silico anti-diabetic study has been published against DPP4, so the goal of this paper is to report on the in silico docking of phytochemicals found in this plant against the target DPP4.

Materials and Methods

Data source

The IMPPAT database (https://cb.imsc.res.in/imppat/home) was used to download phytoconstituents from R. vesicarius and standard drug compounds (3D PDB). The molecular properties were shown in table-1. structure of the selected compounds Apigenin, Chrysophanol, Emodin, Physcion, Catechin, Epicatechin, Luteolin, Quercetin, Rhein, Tetramethylene sulfone, Alloaromadendrene and Cis Limonene oxide showm in figure:1.

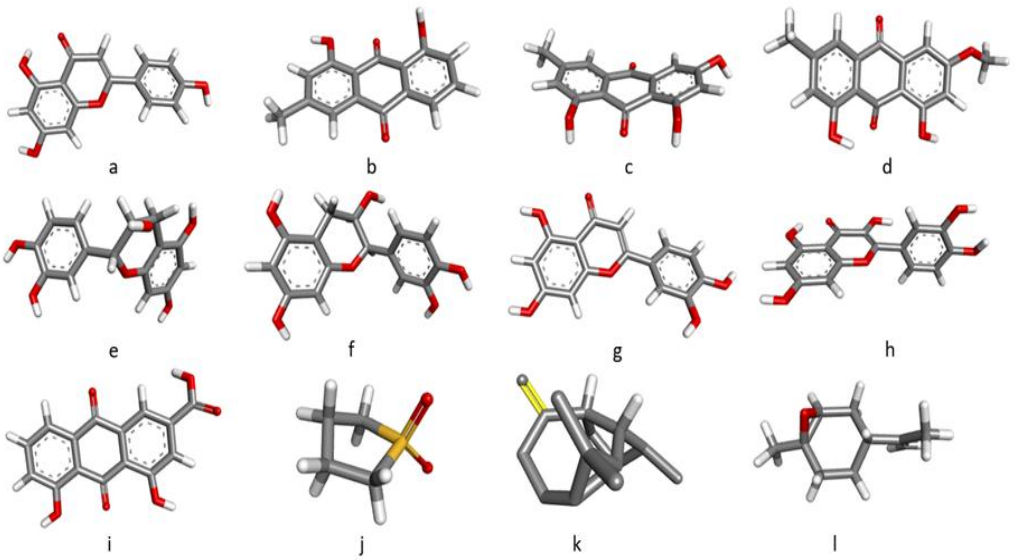

Figure 1. structure of Selected ligands for Docking: a) Apigenin, b) Chrysophanol, c) Emodin, d) Physcion, e) Catechin, f) Epicatechin, g) Luteolin, h) Quercetin, i) Rhein, j) Tetramethylene sulfone, k) Alloaromadendrene and l) Cis Limonene oxide

The current study focuses on the Dipeptidyl peptidase-4 (DPP4) protein in type-2 diabetes mellitus. The method starts with obtaining the structure of the protein, then collecting phytochemicals, and then screening for compounds that are effective and potent against DPP4. The structure of DPP4 was retrieved from the RCSB Protein Databank (https://www.rcsb.org/) in order to target the protein and discover inhibitors (PDB ID: 4A5S). The binding pocket was validated by the presence of an inhibitor, N7F, which was later removed in order to prepare the structure for docking (S Subhani A et al., 2020).

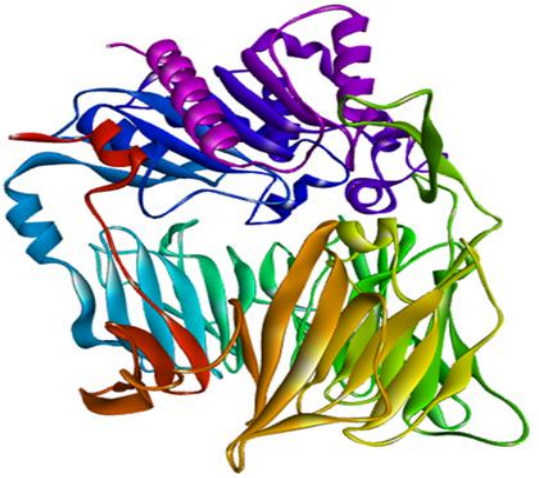

Figure 2. Dipeptidyl peptidase-4 (DPP4): PDB ID: 4A5S

Bioactive score prediction

Drug score values show a compound's overall potential as a drug candidate. Mol inspiration is a web-based application that predicts the bioactivity score of the 40 compounds synthesized against common human receptors as GPCRs, ion channels, kinases, nuclear receptors, proteases, and enzymes.

Evaluation of drug likeliness

Lipinski's rule of five is useful for characterizing the molecular features of medicinal compounds that are needed to estimate critical pharmacokinetic parameters like absorption, distribution, metabolism, excretion, and toxicity (ADMET). The rule is useful in medication development and design. The molsoft server (http://molsoft.com/mprop/) was used to estimate drug similarity and molecular properties.

Docking methodology

Preparation of ligands and protein

Twelve (12) phytoconstituents from R. vesicarius were downloaded from the IMPPAT (https://cb.imsc.res.in/imppat/home) database, PubChem database, and standard drug (Sitagliptin) database. The binding energies of molecules with

DPP4 were calculated using molecular docking. The ligand-receptor complexes were created with optimum conformation in order to monitor the behavior of tiny molecules, typically inhibitors, in the target protein's binding pocket. Further assessments on AutoDock Tools (Rakesh Davella & Estari Mamidala 2021) were used to prepare the retrieved protein for docking. Using AutoDock 4.2, we performed one-by-one molecular docking of DPP4 with several phytochemicals. DPP4 model was created by performing certain crucial editing processes, such as adding polar hydrogen bonds in Auto dock tools, which enabled to change the interactions between phytochemicals and DPP4.

Molecular docking

Autodock 4 was used to dock DPP4 (PDB ID: 4A5S displayed in Figure:2) with selected 12 phytochemical compounds from a total of 40 phytochemicals. Docking server was used to verify the docking computations. The ligand was given partial gustier charges. Rotatable hydrogen bonds were defined after nonpolar hydrogen atoms were combined. The receptor was used to perform docking calculations. The autogrid program was used to build affinity (grid) maps with 25 grid points and 0.500 using essential hydrogen atoms, kollaman charges, and salvation parameters. The van der Waals and electrostatic components were calculated using Autodock settings and distance dependent dielectric functions, respectively (Bikadi Z and Hazai E 2009).

The Lamarckian algorithm (LGA) was used to simulate docking [24]. The drug molecules' initial location torsion and orientation were selected at random. During docking, all rotatable torsions were freed. Each docking experiment was made up of ten separate runs, each of which was programmed to end after 250000 energy calculations (Davella, R et al., 2021). The population was limited to 150 people. The translational step 0.2, as well as the quaternion and torsion step 5, were used during the search.

Results and Discussions

Computational docking is a powerful method for learning about manufactured compounds and their interactions with biological therapeutic targets, which is crucial in drug development. The amino acids in the active site region of the target protein were predicted using the Molecular Docking program.

Evaluation of drug likeliness

Lipinski's rule of five (RO5) is used to assess the druglikeliness of a chemical molecule that possesses qualities that would make it a likely or potential drug in humans (Rakesh Davella and Estari Mamidala 2019). Calculating molecular properties such as log P (partition coefficient), polar surface area, number of hydrogen bond donors, number of hydrogen bond acceptors, and molecular weight might help forecast a pharmacological compound's oral action. According to the rule, the majority of metal complexes with strong membrane permeability have log P 5, ten hydrogen bond acceptors, and five hydrogen bond donors. In general, an orally active medication has no more than one criterion violation. The synthesized ligand and its complexes were found to be in good agreement with the

provided criteria in this investigation, indicating that they have good oral bioavailability.

Table-1 shows the results of a drug likeliness evaluation based on Lipinski's rule of five of 40 ligands. The Lipinski's rule of five is maintained for the majority of ligands based on drug likeliness evaluation.

Table 1
Evaluation of drug likeliness based on Lipinski's rule of five of ligands

S.No.	Compound Name	Molecular formula	Molecular weight	Number of HBA	Number of HBD	Log P
1	apigenin	$C_{15}H_{10}O_5$	270.24	5	3	2.46
2	Chrysophanol	$C_{15}H_{10}O_4$	254.24	4	2	3.54
3	emodin	$C_{15}H_{10}O_5$	270.24	5	3	3.01
4	Isovitexin	$C_{21}H_{20}O_{10}$	432.38	10	7	0.52
5	Orientin	$C_{21}H_{20}O_{11}$	448.38	11	8	0.03
6	Physcion	$C_{16}H_{12}O_5$	284.27	5	2	2.98
7	retinol	$C_{20}H_{30}O$	286.46	1	1	5.92
8	thiamine	$C_{12}H_{17}N_4OS$	265.36	4	3	0.51
9	Vitexin	$C_{21}H_{20}O_{10}$	432.38	10	7	0.52
10	Catechin	$C_{15}H_{14}O_6$	290.08	6	5	1.88
11	Epicatechin	$C_{15}H_{14}O_6$	290.08	6	5	1.88
12	Iso orientin	$C_{15}H_{15}NO_3$	257.11	3	1	1.93
13	Luteolin	$C_{15}H_{10}O_6$	286.05	6	4	2.68
14	Quercetin	$C_{15}H_{10}O_7$	302.04	7	5	2.11
15	Rhein	$C_{15}H_8O_6$	284.03	6	3	2.19
16	2_6-Dimethylundecane	$C_{13}H_{28}$	184.22	0	0	6.38
17	Docosane	$C_{22}H_{46}$	310.36	0	0	10.95
18	Dodecane	$C_{12}H_{26}$	170.20	0	0	6.13
19	Hexacosane	$C_{26}H_{54}$	366.42	0	0	12.88
20	Eicosane	$C_{20}H_{42}$	282.33	0	0	9.98
21	Tetra methylene sulfone	$C_4H_8O_2S$	120.02	2	0	0.44
22	Triacontane	$C_{30}H_{62}$	422.49	0	0	14.80
23	Undecane	$C_{11}H_{24}$	156.19	0	0	5.65
24	Methyl_ laurate	$C_{13}H_{26}O_2$	214.19	2	0	5.08
25	Methyl_ myristate	$C_{15}H_{30}O_2$	242.22	2	0	6.04
26	methyl_ eicosenate	$C_{21}H_{40}O_2$	324.30	2	0	9.08
27	methyl_pentadecanoate	$C_{16}H_{32}O_2$	256.24	2	0	6.52
28	Methyl_palmitate	$C_{17}H_{34}O_2$	270.26	2	0	7.00
29	methyl_margarate	$C_{18}H_{36}O_2$	284.27	2	0	7.49
30	methyl_ linoleate	$C_{19}H_{34}O_2$	294.26	2	0	7.08
31	Methyl_ stearate	$C_{19}H_{38}O_2$	298.29	2	0	7.97
32	Methyl eicosanoate	$C_{22}H_{44}O_2$	340.33	2	0	9.25
33	methyl_dehydro abietate	$C_{21}H_{30}O_2$	314.22	2	0	5.66
34	Methyl docosanoate	$C_{23}H_{46}O_2$	354.35	2	0	9.90
35	methyl_lignocerate	$C_{25}H_{50}O_2$	382.38	2	0	10.86
36	Allo aromadendrene	$C_{15}H_{24}$	204.19	0	0	4.85
37	beta-Elemene	$C_{15}H_{24}$	204.19	0	0	5.39

38	Cadina-1_4-diene	C_{15} H_{24}	204.19	0	0	6.02
39	cis-Limonene	C_{10} H_{16} O	152.12	1	0	2.95
40	Humulene	C_{15} H_{24}	204.19	0	0	5.47

Bioactivity score prediction

The beneficial effects of medications in living beings are referred to as pharmacological activity. A biological target is supposed to bind to the medication. The most frequent proteins used as biological targets include enzymes, ion channels, and receptors. Drug target is another term for biological target. Different characteristics such as binding to G protein-coupled receptor (GPCR) ligand and nuclear receptor ligand, ion channel modulation, kinase inhibition, amaidotransferase inhibition, and enzyme activity inhibition were used to compute the bioactivity scores of the produced complexes. All of the parameters were estimated using the online software Molinspiration (www.molinspiration.com), which predicted that the synthesized complexes will have moderate biological activity. Table-2 shows the bioactivity score. It is known that if the bioactivity score for metal complexes is greater than 0.0, the complex is active; if it is between 5.0 and 0.0, the complex is moderately active; and if it is less than 5.0, the complex is inert.

As shown in Table 2, the bioactivity scores of the ligand and all of the complexes were above 5.0 and 0.0, respectively, indicating that they contain the qualities required for the complexes to act as potential medicines with minor chemical alterations.

Table 2
Bioactivity score of the ligands from *Rumex vesicariu* L

S. No.	Compound	Parameters of Bioactivity score					
		GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1	Apigenin	-0.07	-0.09	0.18	0.34	-0.25	0.26
2	Chrysophanol	-0.23	-0.17	0.06	0.02	-0.26	0.16
3	Emodin	-0.14	-0.14	0.07	0.17	-0.21	0.21
4	Isovitexin	0.12	0.02	0.15	0.23	0.04	0.47
5	Orientin	0.12	-0.14	0.20	0.20	0.01	0.45
6	Physcion	-0.17	-0.23	0.04	0.11	-0.23	0.14
7	Retinol	-0.01	0.32	-0.25	1.02	-0.16	0.66
8	Thiamine	0.26	0.01	-0.37	-1.72	-0.64	1.12
9	Vitexin	0.13	-0.14	0.19	0.23	0.03	0.46
10	catechin	0.41	0.14	0.09	0.60	0.26	0.47
11	Epicatechin	0.41	0.14	0.09	0.60	0.26	0.47
12	Isoorientin	0.11	0.01	0.16	0.20	0.01	0.46
13	Luteolin	-0.02	-0.07	0.26	0.39	-0.22	0.28
14	Quercetin	-0.06	-0.19	0.28	0.36	-0.25	0.28

15	Rhein	-0.08	-0.10	0.01	0.29	-0.06	0.28
16	2_6-Dimethylundecane	-0.57	-0.18	-0.93	-0.67	-0.56	-0.27
17	Docosane	0.02	0.00	-0.07	0.02	-0.02	0.03
18	Dodecane	-0.71	-0.23	-0.93	-0.83	-0.85	-0.35
19	Hexacosane	0.04	0.00	-0.04	0.04	0.04	0.03
20	Icosane	-0.04	0.00	-0.14	-0.05	-0.11	0.03
21	tetramethylene_sulfone	-3.73	-3.88	-3.91	-3.92	-3.56	-3.67
22	Triacontane	0.04	0.00	-0.04	0.04	0.03	0.02
23	Undecane	-0.84	-0.31	-1.08	-0.98	-0.98	-0.44
24	alloaromadendrene	-0.67	-0.47	-0.98	-0.21	-0.67	-0.30
25	beta-elemene	-0.36	0.18	-1.02	0.43	-0.38	0.30
26	Cadina-1_4-diene	-0.33	-0.15	-0.85	-0.09	-0.77	0.19
27	cis- -Limonene_oxide	-0.65	-0.40	-2.04	0.15	-0.63	0.37
28	Humulene	-0.14	0.02	-0.93	0.34	-0.67	0.31
29	Methyl_laurate	-0.41	-0.13	-0.73	-0.43	-0.46	-0.11
30	Methyl myristate	-0.24	-0.07	-0.51	-0.24	-0.28	-0.02
31	methyl_eicosenate	0.02	-0.08	-0.23	0.12	0.07	0.07
32	methyl_pentadecanoate	-0.17	-0.06	-0.42	-0.16	-0.20	0.01
33	Methyl_palmitate	-0.11	-0.05	-0.34	-0.09	-0.13	0.04
34	methyl_margarate	-0.07	-0.05	-0.28	-0.04	-0.08	0.05
35	methyl_linoleate	0.15	0.07	-0.20	0.14	0.03	0.23
36	Methyl_stearate	-0.03	-0.04	-0.23	0.00	-0.03	0.05
37	methyl_eicosanoate	0.03	-0.02	-0.20	0.07	0.14	0.04
38	Methyl dehydroabietate	0.40	0.20	-0.26	0.85	0.02	0.36
39	methyl_docosanoate	0.02	-0.04	-0.16	0.05	0.06	0.04
40	methyl_lignocerate	0.02	-0.04	-0.15	0.05	0.06	0.04

Molecular docking interactions

Twelve phytochemicals were chosen for Docking based on Drug Likeliness and Bioactivity Score of 40 phytochemicals from *R vesicarius*. The 12 selected compounds (Apigenin, Chrysophanol, Emodin, Physcion, Catechin, Epicatechin, Luteolin, Quercetin, Rhein, Tetramethylene sulfone, Alloaromadendrene, and Cis Limonene oxide) were docked into DPP4 enzyme in this study from a total of 40 *R. vesicarius* compounds, and the docking findings were summarized. Out of 12, five compounds Chrysophanol (-8.99 kcal/mol), Physcion (-8.02 kcal/mol), Catechin (-8.20 kcal/mol), Epicatechin (-8.01 kcal/mol), Rhein (-8.22 kcal/mol) showed best score. When docked to DPP4, the molecule Chrysophanol demonstrated higher binding affinity and a best ligand pose energy of -8.99, with the following residues involved in the interaction: VAL:558, ARG:560, LYS:512,554 GLN:527, ASN:562, ASP:545, ALA:564, ILE:529, THR:565, MET:509, PRO:510, LEU:561 PHE:559. GLN:527, ASN:562, ASP:545, ALA:564, ILE:529, THR:565, MET:509, PRO:510, LEU:561 PHE:559.

As a result, among the several chemicals that can block DPP4 from working, the former molecule is an efficient inhibitor. To establish their biological potential, more *in vitro* and *in vivo* studies of individual phytoconstituents are needed. Table-3 shows a ball and socket model of the relevant drug molecule and phytoconstituents interacting with the active site.

Table 3
Docking score and interactions of amino acid residues of Selected 12 Phytochemical compounds of *R. vesicarius* docked against T2DM- DPP4

Sl. N	Compound Name	Binding energy	Inhibition constant	Intermolecular energy	Residue involving interaction	No. of H bonds	Interaction of residues forming H2 bonds
1	Apigenin	-7.89 kcal/mol	1.65 uM	-9.08 kcal/mol	PRO:510, ILE:529, LYS:512,554, ALA:564, PHE:559, VAL:558,575, ARG:560, MET:509, LEU:561, ASN:562, GLN:527	3	PRO:475 ASP:545 THR:565
2	Chrysophanol	-8.99 kcal/mol	256.30 nM	-9.59 kcal/mol	LYS:554 GLN:527, ASN:562, ASP:545, ALA:564, ILE:529, THR:565, MET:509, PRO:510, LEU:561 PHE:559	3	VAL:558 ARG:560 LYS:512
3	Emodin	-7.98 kcal/mol	1.41 uM	-8.88 kcal/mol	VAL:575, PHE:559, SER:511, MET:509, ILE:529, GLN:527, ASP:556,545, ASN:562, ALA:564	6	LYS:512 ARG:560 VAL:558 PRO:510 THR:565
4	Physcion	-8.02 kcal/mol	1.33 uM	-8.91 kcal/mol	PRO:475, LYS:512, ILE:529, ALA:564, PHE:559, VAL:558, GLN:527, THR:565, MET:509, LEU:561,	3	ARG:560 ASN:562 PRO:510
5	Catechin	-8.20 kcal/mol	967.66 nM	-9.99 kcal/mol	ASP:192,200, VAL:254, PRO:255, ILE:193,198, THR:129,199, GLN:153,123, TRP:201,124, SER:127,	5	TYR:195,211 ASN:170, GLU:191,204
6	Epicatechin	-8.01 kcal/mol	1.36 uM	-9.80 kcal/mol	GLU:361,ILE:407,405,375,374,GLY:38,406,HIS:363,VAL:354, PRO:359,PHE:357,LYS:373	6	ARG:356,358 SER:360,376 GLU:347
7	Luteolin	-7.72 kcal/mol	2.18 uM	-9.22 kcal/mol	TRP:157,215,305,THR:199,ALA:210,213, PRO:159,LEU:214	5	TRP:154,216 THR:156 PHE:208 SER:212
8	quercetin	-7.52 kcal/mol	3.09 uM	-9.31 kcal/mol	SER:630,TYR:631,662,666,ARG:125,669,358,ASN:710,	5	SER:209 GLU:205,206 TYR:547

9	Rhein	-8.22 kcal/mol	944.91 nM	-9.41 kcal/mol	TRP:659, GLY:549, PHE:357, VAL:207, VAL: 575, PHE:559, ASN:562,GLN:527,VAL:575,ILE:529,LYS:512, PRO:510, MET:509, ALA:564	4	VAL:558 ARG:560 ASP:545 THR:565
10	tetramethylene_sulfone	-4.78 kcal/mol	315.01 uM	-4.78 kcal/mol	ASN:595, TRP:353, GLY:352,672, GLU:668, ILE:319, ARG:569	2	ASN:321 GLN:320
11	alloaromadendrene	-7.99 kcal/mol	1.39 uM	-7.99 kcal/mol	ASN:420,TYR:585,381,GLU:403,TRP:402,525,ILE:590,THR:401,522,GLN:586,LYS:523,GLY:424,PRO:426,	0	0
12	cis-Limonene o	-6.13 kcal/mol	32.19 uM	-6.43 kcal/mol	PHE:559, SER:511, VAL:558, GLN:527, PRO:510, MET:509, ILE:529, THR:565, LYS:512, ASN:562, ALA:564, ARG:560	0	0
13	Sitaglipti n						

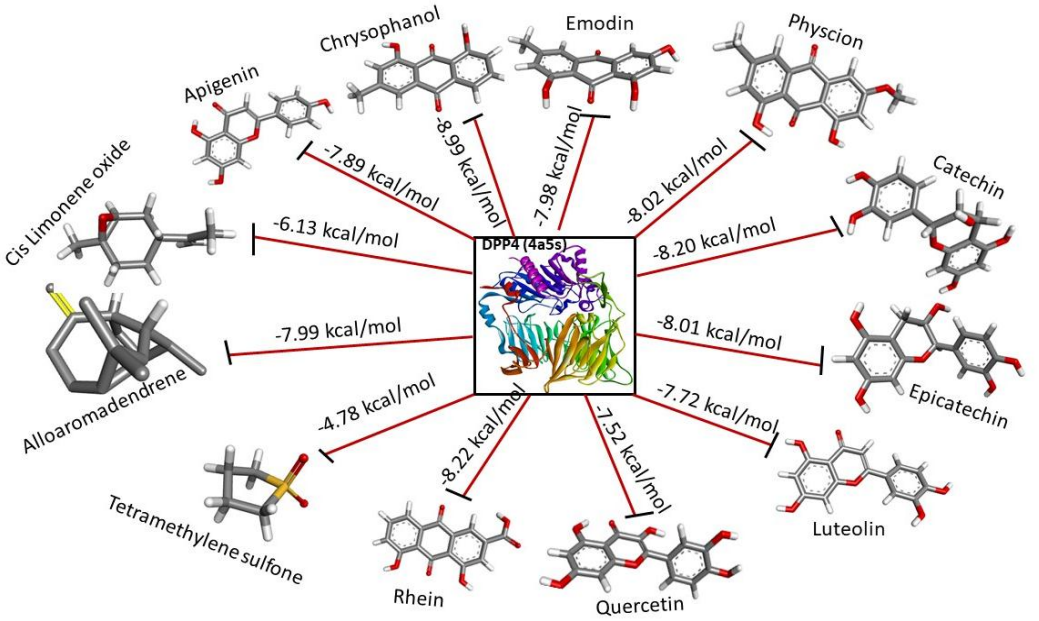

Figure 3. Illustration of ligands from Rumex vesicarius inhibition against the Dipeptidyl peptidase-4 (DPP4).

Binding Interactions of Dipeptidyl peptidase-4 with Chrysophanol

We executed molecular docking studies of Chrysophanol against the Dipeptidyl peptidase-4, shown that, exhibited stable binding with a binding affinity of -8.99 kcal/mol (Table-3). This is attributed to its three conventional hydrogen bonds with VAL:558 ARG:560 and LYS:512 together with hydrophobic interactions with VAL:558, ARG:560, LYS:512,554 GLN:527, ASN:562, ASP:545, ALA:564, ILE:529, THR:565, MET:509, PRO:510, LEU:561 PHE:559 (Figure-4). Based on these observations, the Chrysophanol can be potential Diabetes mellitus inhibitor to combat the Diabetes.

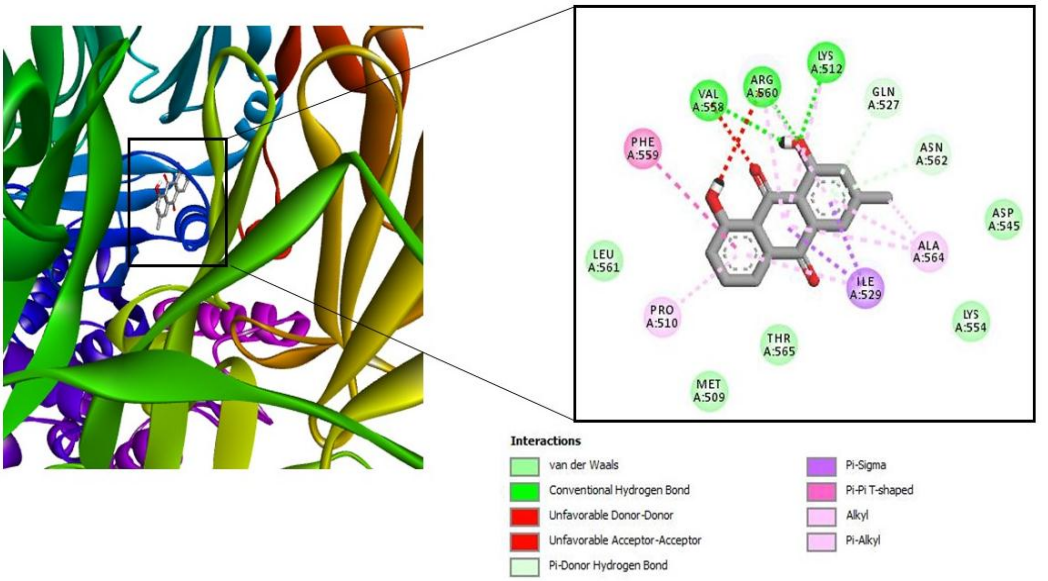

Figure 4. Docking visualization of Dipeptidyl peptidase-4 (DPP4) with Chrysophanol

Binding Interactions of Dipeptidyl peptidase-4 with Physcion

The Physcion shows interaction with the several residues and forms three hydrogen bonds with ARG:560, ASN:562, PRO:510, and thirteen hydrophobic bonds with ARG:560 ASN:562, PRO:510,475, LYS:512, ILE:529, ALA:564, PHE:559, VAL:558, GLN:527, THR:565, MET:509, LEU:561 (Figure-5) and yields the binding energy is -8.02 kcal/mol (Table-3). Based on these results, Physcion can be utilized as drug candidates against diabetes mellitus to inhibit DPP4.

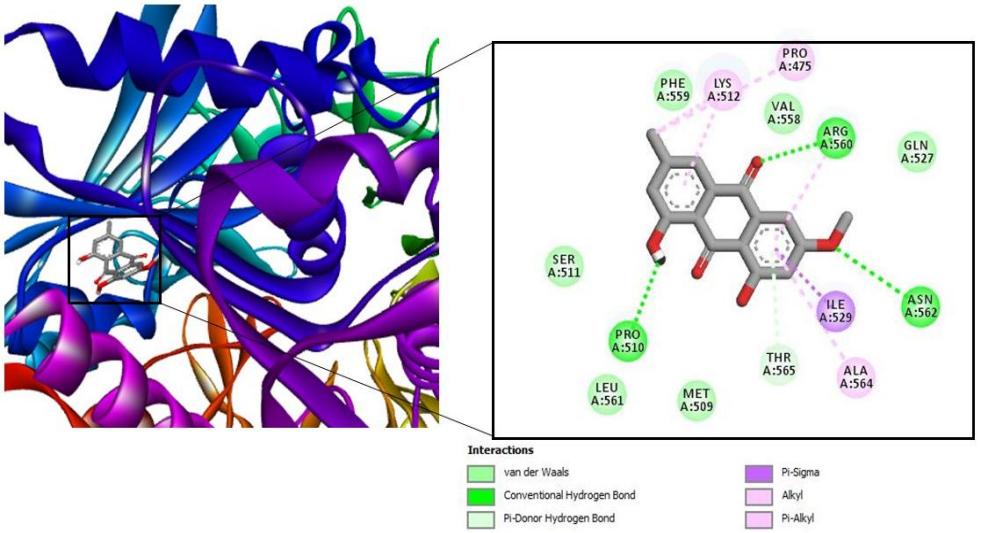

Figure 5. Docking visualization of Dipeptidyl peptidase-4 (DPP4) with Physcion

Binding Interactions of Dipeptidyl peptidase-4 with Catechin

Docking score of the Catechin is tabulated in Table-3. The docking result reveals that, the Catechin has a good binding affinity with – 8.20 kcal/mol on DPP4 and interact with five hydrogen bonds with TYR:195,211 ASN:170, GLU:191,204 of DPP4. The amino acids TYR:195,211, ASN:170, GLU:191,204, ASP:192,200, VAL:254, PRO:255, ILE:193,198, THR:129,199, GLN:153,123, TRP:201,124, SER:127, are hydrophobically interacted with Catechin (Figure-6). The docking results of this study revealed that, Catechin inhibits the action of Dipeptidyl peptidase-4.

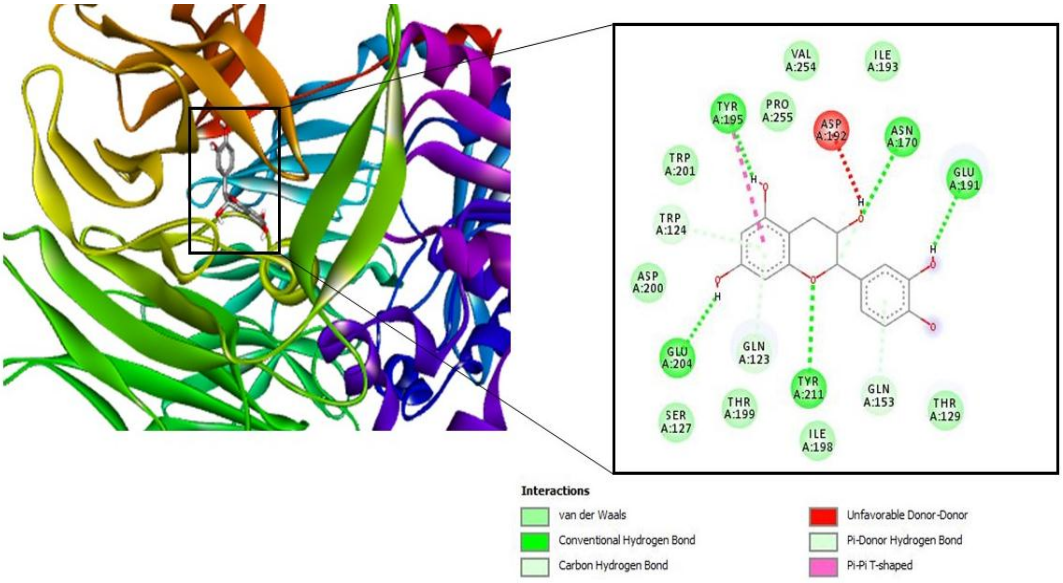

Figure 6. Docking visualization of Dipeptidyl peptidase-4 (DPP4) with Catechin

Binding Interactions of Dipeptidyl peptidase-4 with Epicatechin

Molecular docking using AutoDock, for the Epicatechin was analyzed by BIOVIA Discovery Studio 2016 Visualizer. The Epicatechin displayed binding energy (−8.01 kcal/mol), makes 6 H-bonds with DPP4 was shown in Table-3. Apart from these, hydrophobic interactions are also observed including hotspot residue ARG:356,358, SER:360,376, GLU:347,361, ILE:407, 405,375,374, GLY:382,406, HIS:363, VAL:354, PRO:359, PHE:357, LYS:373 (Figure-7) clearly depicting its ability to bind and block interactions with residues of active site. Analysing these results, it can be observed that Epicatechin exhibited considerably low binding energy with DPP4.

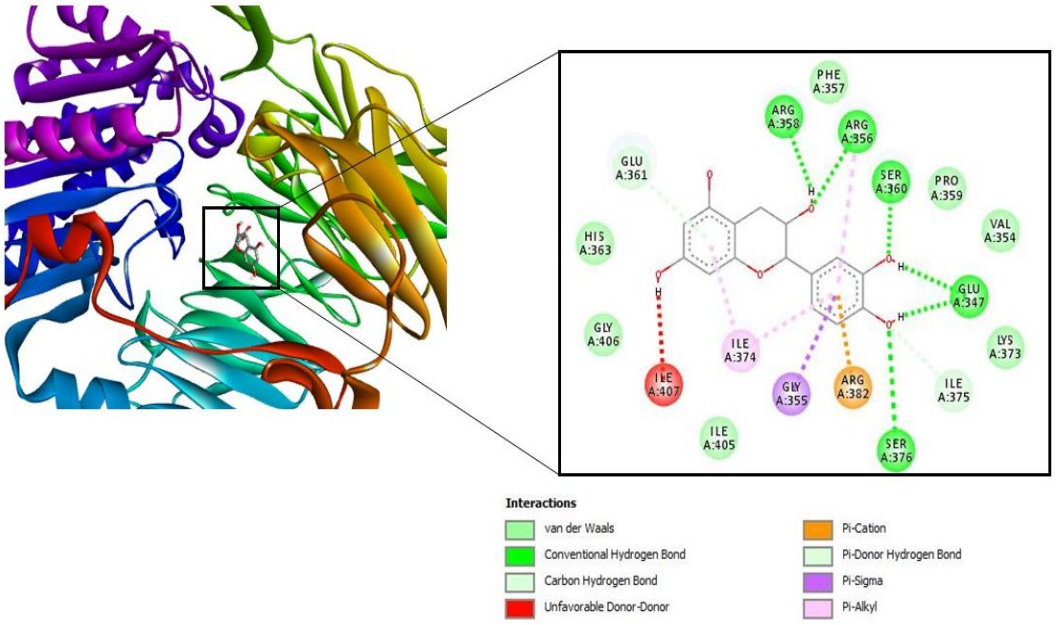

Figure 7. Docking visualization of Dipeptidyl peptidase-4 (DPP4) with Epicatechin

Binding Interactions of Dipeptidyl peptidase-4 with Rhein

From the docking result, the Rhein has binding affinity with (-8.22 kcal/mol) DPP4 and interact with four hydrogen bonds VAL:558 ARG:560 ASP:545 THR:565 of DPP4. The amino acids VAL:558,575, ARG:560, ASP:545, THR:565, PHE:559, ASN:562, GLN:527, VAL:575, ILE:529, LYS:512, PRO:510, MET:509, ALA:564, are hydrophobically interacted with Rhein showed in Figure-8. From this study revealed that, Rhein acts as inhibitor of Dipeptidyl peptidase-

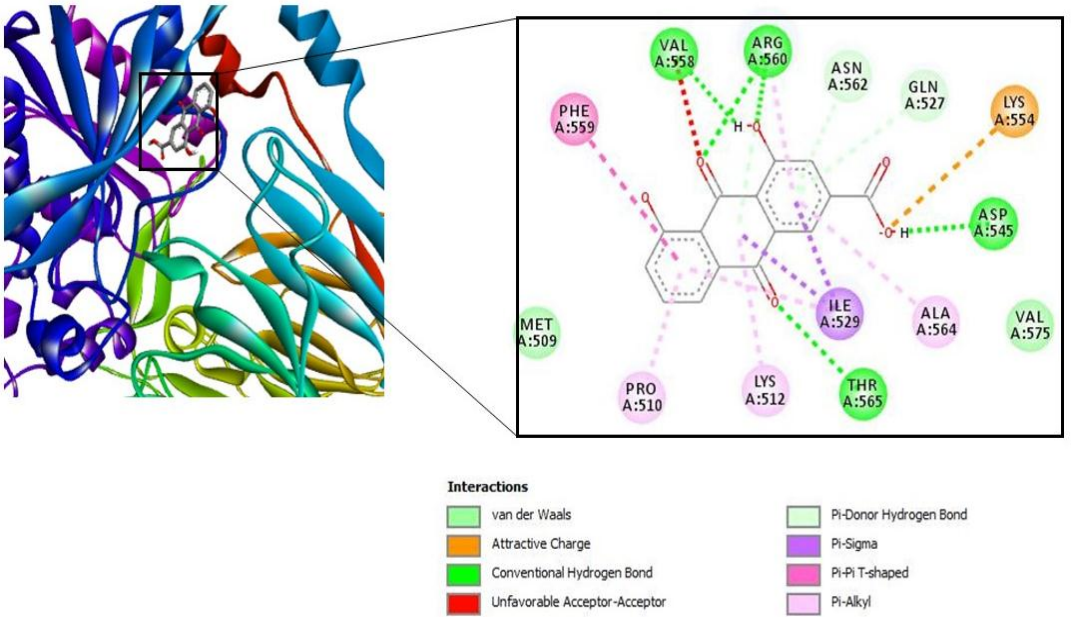

Figure 8. Docking visualization of Dipeptidyl peptidase-4 (DPP4) with Rhein

Conclusion

The major goal of this research was to find a computational medication to combat Dipeptidyl peptidase-4 (DPP4). In this work, 40 phytochemicals from Rumex vesicarius were chosen, 40 of which were screened using good ADMET profiles, and 12 of which were docked. These findings aided in determining the reactivity of the chemicals in question. A comparison with the conventional medicine Sitagliptin (-8.69 kcal/mol) was another crucial aspect of this study. This research identified five chemicals with high binding affinities. Chrysophanol from the Rumex vesicarius plant was found to be the most reactive phytochemical of the twelve, with a binding affinity of -8.99 kcal/mol to DPP4. Following some in-vivo and in-vitro developmental phases, as well as additional tests to confirm their efficacy and safety as a proper and adequate medicine against DPP4, with no health risks.

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References

Abutbul S, Golan G, Barzani O, 2fir R, Zilberg D (2005) Screening of desert plants for use against bacterial pathogens in fish Israeli J Aquaculture Bamidgeh 57: 71-80. http://hdl.handle.net/10524/19132

Al-Qura'n S. (2009). Ethnopharmacological survey of wild medicinal plants in Showbak, Jordan. Journal of ethnopharmacology, 123(1), 45–50. https://doi.org/10.1016/j.jep.2009.02.031

Bikadi, Z., & Hazai, E. (2009). Application of the PM6 semi-empirical method to modeling proteins enhances docking accuracy of AutoDock. Journal of cheminformatics, 1, 15. https://doi.org/10.1186/1758-2946-1-15

Chase, M. & Reveal, A. [2009]. An update of the Angiosperm Phylogeny Group classification for the orders and families of flowering plants: APG III. Botanical Journal of Linnaean Society 161(2): 105- 121. https://doi.org/10.1111/j.1095-8339.2009.00996.x

Davella, R., & Mamidala, E. (2021). Luteolin: A Potential Multiple Targeted Drug Effectively Inhibits Diabetes Mellitus Protein Targets. Journal of Pharmaceutical Research International, 33(44B), 161-171. https://doi.org/10.9734/jpri/2021/v33i44B32661

Davella, R., Gurrapu, S., & Mamidala, E. (2021). Phenolic compounds as promising drug candidates against COVID-19 - An integrated molecular docking and dynamics simulation study. Materials today. Proceedings, 10.1016/j.matpr.2021.05.595. Advance online publication. https://doi.org/10.1016/j.matpr.2021.05.595

Drucker D. J. (2003). Therapeutic potential of dipeptidyl peptidase IV inhibitors for the treatment of type 2 diabetes. Expert opinion on investigational drugs, 12(1), 87–100. https://doi.org/10.1517/13543784.12.1.87

Ebert, R., & Creutzfeldt, W. (1987). Gastrointestinal peptides and insulin secretion. Diabetes/metabolism reviews, 3(1), 1–26. https://doi.org/10.1002/dmr.5610030101

Elegami, A. A., Almagboul, A. Z., Omer, M. E., & El Tohami, M. S. (2001). Sudanese plants used in folkloric medicine: screening for antibacterial activity. Part X. Fitoterapia, 72(7), 810–817. https://doi.org/10.1016/s0367-326x(01)00310-0

Farngren, J., Persson, M., Schweizer, A., Foley, J. E., & Ahrén, B. (2014). Glucagon dynamics during hypoglycaemia and food-re-challenge following treatment with vildagliptin in insulin-treated patients with type 2 diabetes. Diabetes, obesity & metabolism, 16(9), 812–818. https://doi.org/10.1111/dom.12284

He, Z. X., Zhou, Z. W., Yang, Y., Yang, T., Pan, S. Y., Qiu, J. X., & Zhou, S. F. (2015). Overview of clinically approved oral antidiabetic agents for the treatment of type 2 diabetes mellitus. Clinical and experimental pharmacology & physiology, 42(2), 125–138. https://doi.org/10.1111/1440-1681.12332

Heywood, V.H. 1978. Flowering Plants of the World. Oxford University Press Oxford: 336 pp. https://www.scirp.org/(S(czeh2tfqyw2orz553k1w0r45))/reference/ReferencesPapers.aspx?ReferenceID=386480

Holst J. J. (2007). The physiology of glucagon-like peptide 1. Physiological reviews, 87(4), 1409–1439. https://doi.org/10.1152/physrev.00034.2006

International Diabetes Federation. IDF Diabetes Atlas 8th edition., http://www.diabetesatlas.org (Accessed November 14, 2017). https://ncdalliance.org/resources/diabetes-atlas-2017-is-now-online

Kannel, W. B., & McGee, D. L. (1979). Diabetes and cardiovascular risk factors: the Framingham study. Circulation, 59(1), 8–13. https://doi.org/10.1161/01.cir.59.1.8

Prasuna, C. P., Chakradhar, R. P., Rao, J. L., & Gopal, N. O. (2009). EPR and IR spectral investigations on some leafy vegetables of Indian origin.

Spectrochimica acta. Part A, Molecular and biomolecular spectroscopy, 74(1), 140–147. https://doi.org/10.1016/j.saa.2009.05.020

Rahman, M. A., Mossa, J. S., Al-Said, M. S., & Al-Yahya, M. A. (2004). Medicinal plant diversity in the flora of Saudi Arabia 1: a report on seven plant families. Fitoterapia, 75(2), 149–161. https://doi.org/10.1016/j.fitote.2003.12.012

Rakesh Davella and Estari Mamidala (2019). Molecular docking of flavonoids from Rumex vesicarius with FOXO1 target related to Diabetes mellitus Biolife. 7(4). DOI:10.17812/blj.2019.7402. retrieved from https://www.scribd.com/document/529947680

Rakesh Davella, Estari Mamidala. (2021). Molecular Docking and Dynamic Simulation Studies of compounds from Rumex vesicarius against Maltase-Glucoamylase to treat type 2 Diabetes. Annals of the Romanian Society for Cell Biology25(6), 21062–21077. Retrieved from, https://www.annalsofrscb.ro/index.php/journal/article/view/10565

Rasmussen, H. B., Branner, S., Wiberg, F. C., & Wagtmann, N. (2003). Crystal structure of human dipeptidyl peptidase IV/CD26 in complex with a substrate analog. Nature structural biology, 10(1), 19–25. https://doi.org/10.1038/nsb882

S Subhani A, Arif N, Hussain W, Rasool N. [2020] In silico discovery of potential inhibitors against Dipeptidyl Peptidase-4: A major biological target of Type-2 diabetes mellitus. Int J Clin Microbiol Biochem Technol. 3: 001-010 https://doi.org/10.29328/journal.ijcmbt.1001008

Sanchez, A., & Kron, K. A. (2008). Phylogenetics of Polygonaceae with an Emphasis on the Evolution of Eriogonoideae. Systematic Botany, 33(1), 87–96. http://www.jstor.org/stable/25064320

Stein, S. A., Lamos, E. M., & Davis, S. N. (2013). A review of the efficacy and safety of oral antidiabetic drugs. Expert opinion on drug safety, 12(2), 153–175. https://doi.org/10.1517/14740338.2013.752813

Trott, O., & Olson, A. J. (2010). AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. Journal of computational chemistry, 31(2), 455–461. https://doi.org/10.1002/jcc.21334

Wu, T., Rayner, C. K., & Horowitz, M. (2016). Inter-regulation of gastric emptying and incretin hormone secretion: implications for postprandial glycemic control. Biomarkers in medicine, 10(11), 1167–1179. https://doi.org/10.2217/bmm-2016-0164

Yasmin, G., Khan, M.A., Shaheen, N., & Hayat, M.Q. (2010). Micromorphological investigation of foliar anatomy of Fagopyrum Mill., and Rumex L. of Polygonaceae. Pakistan Journal of Botany, 42, 47-57. http://www.pakbs.org/pjbot/PDFs/42(1)/PJB42(1)047.pdf